MicroRNA-223 dose levels fine tune proliferation and differentiation in human cord blood progenitors and acute myeloid leukemia.

Abstract:
A precise understanding of the role of miR-223 in human hematopoiesis and in the pathogenesis of acute myeloid leukemia (AML) is still lacking. By measuring miR-223 expression in blasts from 115 AML patients, we found significantly higher miR-223 levels in patients with favorable prognosis, whereas patients with low miR-223 expression levels were associated with worse outcome. Furthermore, miR-223 was hierarchically expressed in AML subpopulations, with lower expression in leukemic stem cell-containing fractions. Genetic depletion of miR-223 decreased the leukemia initiating cell (LIC) frequency in a myelomonocytic AML mouse model, but it was not mandatory for rapid-onset AML. To relate these observations to physiologic myeloid differentiation, we knocked down or ectopically expressed miR-223 in cord-blood CD34? cells using lentiviral vectors. Although miR-223 knockdown delayed myeloerythroid precursor differentiation in vitro, it increased
myeloid progenitors in vivo following serial xenotransplantation. Ectopic miR-223 expression increased erythropoiesis, T lymphopoiesis, and early B lymphopoiesis in vivo. These findings broaden the role of miR-223 as a regulator of the expansion/differentiation equilibrium in hematopoietic stem and progenitor cells where its impact is dose- and differentiation-stage-dependent. This also explains the complex yet minor role of miR-223 in AML, a heterogeneous disease with variable degree of myeloid differentiation.